REMARKS

Claims 1-14, 16, 18 are presently pending. Claims 1-8, 12, 13, 16 have been amended. Claims 15 and 17 have been cancelled. No new matter has been added to this application by way of amendment. Applicants confirm the election of Group I of the restriction as stated on page 2 of the present office action:

Ar1 is claim 3 definitions;

All R no hetero rings, no forming hetero rings;

J is alkyl;

W is CH;

Y is N;

Q is CR^p.

Claims 15-17 have been rejected under 35 USC 112, first paragraph. It is alleged that the specification while being enabled for inflammation does not reasonably provide enablement for all oncological diseases or the other specifically recited diseases in claims 16 and 17. This rejection is traversed in-part.

Applicants traverse the rejection with respect to the other recited diseases in claims 16. It is also stated in the Office Action, paragraph 3, that only inflammation is enabled. As taught in the specification on page 1 and elsewhere, the compounds of the invention inhibit production of cytokines involved in inflammatory processes and are thus useful for treating diseases and pathological conditions involving inflammation. Applicants respectfully request that the Office provide evidence or sound scientific reasoning on the record as to why the method claims are enabled for treating some diseases under the category of 'inflammation', and not the other claimed diseases. Also, the Examiner has not identified to applicants which inflammatory diseases are not enabled. Without such evidence, this determination is apparently arbitrary and without the substantiation as required by law. ***In re Marzocchi***, 169 USPQ 367 (CCPA 1971).

The Examiner alleges on pages 3-4 that the claimed invention is not commensurate in scope with the enablement. Applicants strongly disagree. The issue of the scope of the claims being commensurate with the enablement was before the court in ***In re Fisher*** 166 USPQ 18 (CCPA 1970. In that case, the CCPA in justifying it's conclusion that the claims were not commensurate in scope with the enablement, stated that in cases involving unpredictable factors such as chemical reactions and physiological activity the scope of enablement varies inversely with the degree of unpredictability of the factors involved. The CCPA expressed the identical sentiment in its decision in ***In re Marzocchi*** 169 USPQ 367 (CCPA 1971). However the court in the ***In re Marzocchi*** decision also required that the Office, in order to establish a prima facie case of nonenablement, must explain why the specification is not enabled based on sound scientific reasoning or acceptable evidence which is inconsistent which the asserted statement.

Here, other then broad generalizations on page 4 of the office action, no reasons specific to the present claims have been provided by the Examiner based on sound scientific reasoning or acceptable evidence why one of ordinary skill in the art would doubt the asserted statement in the specification with respect to the claimed diseases. As stated above, the Office has not identified to applicants which inflammatory diseases are not enabled and which are enabled. As such, the specification is assumed to be in compliance with the enablement requirement for these diseases.

Regarding the caffeine analogy given by the Examiner as an example to allege nonenablement, it is not clear how this reasoning is relevant to the instant small molecules possessing anti-cytokine activity and the claimed uses thereof.

The discussion in the Background section provides references which create the nexus between the activity possessed by the instant compounds and the claimed diseases. In addition, Applicants provide further evidence in the IDS submitted herewith establishing a correlation between the presently claimed diseases and asserted activity in the specification. Several of the references below are also cited in the Background section. A summary of each is provided below.

Rheumatoid Arthritis, Crohn's disease, Behcet's disease, Ankylosing spondylitis. Early Alert Report, Fall 2000. This article reviews TNFα inhibitors, both biological and small molecule, and discusses their uses in the aforementioned diseases.

Inflammatory bowel disease, Ulcerative Colitis: van Heel et al., *Human Molecular Genetics* (2002) discloses that IBD is characterized by increased levels of TNFα and that anti-TNF therapy is efficacious in treating the disease.

Osteoarthritis: A study by G.R. Webb et al., *Osteoarthritis and Cartilage*, 1997, 5, 427, showed that cartilage in explants from knee joints from osteoarthritic patients was more susceptible to degradation stimulated by TNFα than in explants from non-arthritic patients, suggesting a role for TNFα in osteoarthritis.

Multiple sclerosis: A role for TNFα in multiple sclerosis is suggested by the finding that levels of TNFα correlate with disease progression (C.S. Raine et al., *Rev. Neurol.* (Paris) 1998, 154, 577).

Guillain-Barre Syndrome: A study of genetic polymorphisms in patients with Guillain-Barre Syndrome showed higher frequency of an allele associated with high TNFα production suggesting a role for TNFα in that disease (J.J. Ma et al., *Annals of Neurology*, 1998, 44, 815).

Psoriasis: G. Chodorowska, *J. Eur. Acad. Dermatol. And Venesol.*, 1998, 10, 147, indicates that TNFα and INF-γ have important roles in the inflammatory process of psoriasis.

Graft-versus-host disease (GVHD): in a study of patients who have undegone allogenic bone marrow transplantation, A. Nagler et al., *Cytokines, Cellular & Molecular Ther.*, 1998, 4, 161, found a positive correlation between elevated TNFα levels and development of GVHD. They also mentioned that an anti-TNFα antibody has shown encouraging results in preventing GVHD.

Systemic lupus erythematosus (SLE): in a study of patients with SLE, E. Robak found that levels of TNFα were elevated in SLE patients compared to normal controls and also that there was a correlation between levels of TNFα and disease activity. Robak, E. *Archivum Immunologiae et Therapiae Experimentalis*, 1998, 46,375-380.

Restenosis after Percutaneous transluminal coronary angioplasty (PCTA): a patient study discussed in the paper indicates that proinflammatory cytokines, six including TNFα, are associated with restenosis after PCTA. Tashiro, H. et al. *Coronary Artery Disease*, 12:107-113.

Diabetes: TNFα has been reported to play a key role in insulin resistance leading to type II diabetes (P. Storz et al., *FEBS Letters*, 1998, 440, 41). Inhibition of TNFα has been shown to be protective against Type I diabetes in non-obese diabetic mice as well (G.R. Brown et. al., *Diabetologia*, 1998, 41, 1502).

Toxic shock syndrome and sepsis: in a study with mouse monocytes and lymphocytes, treatment of these cells with an immunomodulator suppressed formation of TNFα upon stimulation of these cells with toxic shock syndrome toxin 1 (J. Soltys and M.T. Quinn, *Infection and Immunity*, 1999, 244). The authors suggest that treatment with agents that reduce levels of proinflammatory cytokines such as TNFα can be beneficial in toxic shock syndrome and sepsis.

Alzheimer's disease: K.B. Bjugstad et al., *Brain Research,* 1998, 795, 349, reported that in patients with AIDS dementia complex levels of TNFα are consistently elevated. They also report that enhanced levels of TNFα have been found in the brains of patients with Alzheimer's disease and suggest that the inflammation brought about by TNFα may be responsible for damage in these neurodegenerative diseases.

Chronic neuropathic pain: R.C. Chou et al., *J. Neuroimmunol.*, 1998, 82, 140, report that release of TNFα, regulated by an adrenergic mechanism contributes to the pathogenesis of several models of chronic neuropathic pain.

Contact Dermatitis: a review article discusses studies which indicate that allergic contact dermatitis and irritant contact dermatitis are characterized by different cytokine patterns which seem to be highly specific. Muller, G. *American Journal of Contact Dermitis*. Vol 7, No.3 (September), 1996: pp 177-184.

Atherosclerosis : A study suggests a crucial role for TNF in females and IL-1 in both sexes during the initial step of the atherosclerotic process of a mouse model. Elhage, R. *Circulation*. 1998; 97:242:244.

Glomerulonephritis: using TNFα deficient mice and a model of glomerulonephritis, B. Ryffel et al., *Int. J. Exp. Path.*, 1998, 79, 453, found that TNFα plays a key role in recruitment of inflammatory cells and subsequent development of glomerulonephritis.

Reperfusion injury:

Nerve Injury: a study by Mitsui, Y. et al. *Brain Research* 844 (1999) 192-195, supports the notion that TNFα and IL-1beta are involved in the inflammatory response of ischemia-reperfusion injury to the peripheral nervous system.

Renal ischemia: a study focusing on (MIP)-2, mentions that IL-1beta, and to a lesser extent TNFα, were expressed in a murine model of ischemia-reperfusion injury. Lemay. S. et al. *Transplantation*, Vol 69, 959-963, No. 5, March 15, 2000.

Intestinal ischemia-reperfusion injury: Intestinal I/R injury is commonly associated with injury to remote organs from the initial site. Borjession, A. et al. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 278:L3-L12, 2000, reports that injury to the lungs after intestinal injury may be due in-part to TNFα.

Osteoporosis: A report by K. Kurokouchi et al., *J. Bone and Mineral Res.*, 1998, 13, 1290., suggests that TNFα plays an important role in the production of cytokines and cell adhesion molecules in osteoblasts leading to bone resorption and inflammation in osteoporosis.

Chronic Obstructive Pulmonary Disease (COPD): the major cause COPD is smoking. Less common are genetic factors which contribute to COPD. Certain genetic factors were studied by Higham et al. *Eur Respir J 2000*; 15:281-284 which concluded that while an association between the TNF2 allele and an increases risk of developing COPD was established in a male Taiwanese population, such a correlation was not demonstrated in a Caucasian population of smokers. Takabatake, N. et al. *Am J Respir Crit Care Med.* Vol 161 pp 1179-1184, 2000, obtained data suggesting that systemic hypoxemia noted in patients with COPD is associated with activation of the TNFα system *in vivo*.

Asthma: in vivo studies suggest evidence for cytokine involvement in asthma, these cytokines include GM-CSF, IL-3, IL-4,IL-5, IL-6 and TNFα. Lee, TH. *Journal of the Royal College of Physicians of London*. Vol 32 No.1, Jan/Feb 1998, pp56-64.

Stroke: J.M. Lipton et al., *Neuroimmunomodulation,* 1998, 5, 178, report that TNFα contributes to the inflammatory processes responsible for neurodegenerative diseases including stroke.

Myocardial infarction (MI): a study by D. Li et al., *Amer. Heart Journal*, 1999, 137, 1145, found TNFα levels increased in patients with myocardial infarction (MI). In a further study with a rabbit model of MI, a TNFα antibody reduced the size of necrosis. The study suggests that TNFα contributes to myocardial injury and treatment with an agent that inhibits TNFα can be cardioprotective in MI.

Thermal injury: in a study of burn patients (F.L. Yeh et al., *Burns*, 1997, 23, 6) TNFα levels were found to be elevated, with highest levels in patients who did not survive. The

authors suggest that inhibition of exaggerated production of TNFα would be beneficial in treatment of thermal injury.

Adult respiratory distress syndrome (ARDS): a study in guinea pigs and rats (L.M. Renzetti and P.R. Gater, *Inflamm. Res.* 1997, 46, Suppl. 2, S143) suggested that compounds that inhibit TNFα may be useful in treating a number of pulmonary diseases including ARDS.

Multiple organ injury: in a study with rats S. Bahrami et al., *Am. J. Physiol*, 1997, 272 (*Heart Circ. Physiol.* 41), H2219, suggested that TNFα is an important mediator in multiple organ injury following a traumatic insult (hemorrhagic shock), the paper indicates that treatment with inhibitors such as monoclonal antibodies to TNFα would be beneficial.

Dermatoses: F. Ameglio et al., *J. Biol. Regul. Homeost. Agents*, 1997, 11, 148, found that TNFα serum levels were increased in dermatoses including bullous pemphigoid and pemphigus vulgaris, and levels correlated with the number of lesions.

Meningitis: in a rabbit model of meningitis, M.M. Paris et al., *J. Infectious Dis.*, 1997, 176, 1239, showed that the anti-inflammatory cytokine IL-10 reduced the level of TNFα in the cerebrospinal fluid. The authors suggest that agents that can do this may be beneficial in modulation, the inflammatory response in meningitis.

Necrotizing enterocolitis: R.M. Viscardi et al., *Pediatric Pathol. And Lab. Medicine,* 1997, 17, 547, found higher level of mRNA for TNFα in intestinal sections of infants with necrotizing enterocolitis, suggesting that it is one of the inflammatory cytokines involved in augmentation of the inflammatory response in this disease.

In the Office Action, on page 4, it is alleged that very little direction is given in the specification for treating all the claimed diseases with the instant compounds. For all the reasons provided above, applicants disagree. The first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of

enablement provided by the specification. Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. ***In re Marzocchi, id at 369***.

The section entitled "Methods of Use" teaches methods known to those of ordinary skill in the art for administration, dosage level, dosage form and formulation and further provides guidance in each of the aforementioned by teaching the respective preferred methods. Specifically, with respect to formulations, on page 91, it is taught that pharmaceutical compositions comprising compounds of the invention contain at least about 5%, but more preferably at least about 20%, of a compound of the invention (w/w). The next paragraph provides guidance on particular pharmaceutical carriers and adjuvants used in formulations. It is also taught that "[t]he optimum percentage (w/w) of a compound of the invention may vary and is within the purview of those skilled in the art."

For the dosage form and preparation, Applicants have taught that known methods can be used and in particular have made reference to H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). It is further taught that dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. Here, it is specifically taught that in some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient, that up to 5 doses per day may be given, and that for oral doses, up to 2000 mg/day may be required. It is then taught, as the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors, which are described thereafter. As stated above, Applicants have provided adequate teaching and guidance to test the instant compound for anti-cytokine activity. Using the THP cell assay on page 92, the ordinary artisan can determine preferred compounds which inhibit TNFα production, further guidance is provided by teaching that preferred compounds will exhibit an $IC_{50} < 10$ uM. In further support of applicants' enablement in the present specification, also submit herewith is Branger et al., (2002) *J Immunol.* 168: 4070-4077. This article discloses

human endotoxin studies with specific dosage forms of example no. 8 (referred to as BIRB 796 BS in the paper) of US 6,319,921. The compound is chemically described on the bottom of column 2, first page of Branger et al. This is provided to the Examiner as evidence that the THP cell assay in the present specification is one of a number of art recognized methods used in calculating a therapeutic index. On page 4071, first column, "Effect of BIRB 796 BS on p38 MAPK activation in vitro" in the methods, and at figure 1, the concept of *ex vivo* challenge of whole blood (containing monocytic cells similar to the THP cell line used in the assay in the instant specification) was used to indicate potential efficacy in the clinic. The paper also provides a teaching of dosage and formulation of BIRB 796 BS. This publication varies, for clinical use, the LPS challenged THP cell assay described in the present specification. The variation is that the Branger *in vitro* LPS challenged cell assay uses PBMC (another human white blood cell cell type) instead of THP cells.

Applicants contend therefore that by using the teaching and guidance in the specification, including the art recognized THP cell assay described therein, together with known methods in the art such as those described herein-above, one of ordinary skill in the art can practice the claimed invention without undue experimentation.

In view of the foregoing, the claimed invention is believed to be in compliance with 35 USC 112, first paragraph. Withdrawal of the rejection of the present claims is therefore proper and respectfully requested.

Claims 18 has been rejected under 35 USC 112, second paragraph. This rejection is traversed.

Applicants disagree that the claimed process is ambiguous and does not recite steps. The claim language clearly recites the following process steps (with underline added for emphasis):
coupling under suitable conditions an amine bearing Ar^1 carboxylic acid of the formula (III), where P is a protecting group,

removing the protecting group P to provide an intermediate of formula (V) under suitable conditions;

coupling under suitable conditions the intermediate (V) with a halo heterocycle VI (Z = halogen) bearing R^6 in the presence of a suitable base to provide a compound of the formula (I).

Regarding suitable conditions, scheme I on pages 57-58 provides a clear description on what is intended by suitable conditions in the form of examples and a literature reference, and teaches that the compounds may also be prepared by analogous methods which will be apparent to one of ordinary skill in the art. In view of what is disclosed in the application and what is known in the art, applicants therefore contend that one of ordinary skill in the art would be able to ascertain the metes and bounds of the claims.

In view of the foregoing, the claimed invention is believed to be in compliance with 35 USC 112, second paragraph. Withdrawal of the rejection of the present claims is therefore proper and respectfully requested.

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